JACC Vol. 31, No. 7
June 1998:1534–9

Unstable Angina: Good Long-Term Outcome After a Complicated Early Course

RON T. VAN DOMBURG, PHD, ADDY J. VAN MILTENBURG-VAN ZIJL, MD, PHD, RINUS J. VEERHOEK, MD,* MAARTEN L. SIMOONS, MD, PHD, FACC

Rotterdam, The Netherlands

Objectives. **This study was performed to investigate the long-term outcome of patients with unstable angina within subgroups of the Braunwald classification.**

Background. **Long-term follow-up studies of patients with unstable angina are rare and date from more than two decades ago. This study was performed to establish the prognosis of different subgroups of patients with unstable angina (Braunwald criteria) during a 7-year follow-up period.**

Methods. **We registered a well defined group of 417 consecutive patients, admitted to the hospital for suspected unstable angina. The definite diagnosis was unstable angina in 282 patients (68%) and evolving myocardial infarction in 26; in 109 patients (26%), the symptoms were attributed to other or nonspecific causes. Patients with definite unstable angina were subclassified according to the Braunwald classification. Survival, survival without infarction and survival without infarction or intervention were determined for each class.**

Results. **After a median follow-up period of 94 months, the mortality rate in the first year was 6% and 2% to 3% in the following years. The frequency of revascularization was 47% in the first year, and that for myocardial infarction was 11% in the first year and 1% to 3% thereafter. The Braunwald classification appeared to be appropriate for risk stratification in the first year. However, at 7 years the event rates in all classes were similar. In particular, the Braunwald classification had no long-term impact on mortality or infarction rates. However, patients with acute angina at rest or postinfarction angina and patients with extensive anginal treatment had high intervention rates.**

Conclusions. **To our knowledge, this study is the first to demonstrate that despite a complicated course during the first year, current management results in good long-term outcome in patients with unstable angina.**

(J Am Coll Cardiol 1998;31:1534–9)

The onset of unstable angina portends a significant risk for the occurrence of major cardiac events, including death and myocardial infarction. In previous studies (1–3), 1-year mortality rates varied from 2% to 18% and 1-year myocardial infarction rates from 7% to 21%. Long-term follow-up reports of patients with unstable angina are rare (4). We report the 7-year follow-up results of 282 consecutive patients who were admitted with unstable angina, to establish the incidence and prognosis of the various subgroups of unstable angina. The Braunwald classification (5) appeared to be an appropriate instrument for identifying groups of patients with different levels of risk at 6 months (6). The validity of this classification for longer term follow-up was assessed.

Methods

Classification of patient groups. During a 7-month period in 1988 and 1989, a prospective registry was maintained in two hospitals in Rotterdam. Four hundred seventeen consecutive patients with suspected unstable angina, according to the attending physician, were included in the study. The admission diagnosis, *suspected unstable angina*, was based on a history of chest pain at rest or at minimal exertion, probably of ischemic origin, without signs of acute infarction or other causes of chest pain. Electrocardiographic (ECG) changes were not required for inclusion. Secondary referrals from other hospitals for treatment were excluded. The final diagnosis as registered 24 to 48 hours after admission was based on evolution of symptoms and documentation of objective ECG criteria during observation or elevated enzyme levels. Three final diagnoses were determined: acute myocardial infarction, definite unstable angina and atypical chest pain or other disease (7). A final diagnosis of *myocardial infarction* was defined as the occurrence of serum creatine kinase levels above twice the local upper limit of normal. *Definite unstable angina* was based on the assessment of symptoms and on documentation of ECG changes (see Data collection). Patients with an initial infarction who had recurrent anginal pain after 24 h were classified as having postinfarction unstable angina. For patients with definite unstable angina, the final classification was made after 24 to 48 h of observation according to the Braunwald classification of unstable angina (5): *Severity* = new onset of severe or accelerated angina without pain at rest (*class I* = no rest pain);

From the Thoraxcenter, Erasmus University and University Hospital Rotterdam and *Sint Franciscus Hospital, Rotterdam, The Netherlands.

Manuscript received September 23, 1997; revised manuscript received February 24, 1998, accepted March 4, 1998.

Address for correspondence: Dr. Ron T. van Domburg, University Hospital Rotterdam, Thoraxcenter, Room Bd 308, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: vandomburg@thch.azr.nl.

0735-1097/98/$19.00
PII S0735-1097(98)00140-5

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
ECG = electrocardiogram, electrocardiographic
PTCA = percutanous transluminal coronary angioplasty

angina at rest within the past month but not within the preceding 48 h (*class II* = subacute angina at rest); or angina at rest within 48 h (*class III* = acute angina at rest). *Clinical circumstances* = unstable angina in the absence of an extracardiac condition (*class B* = primary unstable angina) or that developed within 2 weeks after acute myocardial infarction (*class C* = postinfarction unstable angina). Patients with secondary angina, related to noncardiac conditions (*class A*), were excluded from the analysis. *ECG changes* = present or absent. *Intensity of treatment* = none or one of the major antianginal drugs, beta-adrenergic blocking agents, long-acting nitrates and calcium antagonists (minimal therapy); more than one of these drugs (extensive oral therapy) or extensive use of antianginal therapy, including intravenous nitrates (maximal therapy).

Data collection. The data were prospectively collected and focused on the various decision moments during the hospital stay. Demographic data, history and characteristics of presentation were recorded at admission. During the hospital period, a log was kept of new pain episodes, new infarction or death and diagnostic and therapeutic measurements, such as ECG findings, exercise tests results, medication and intervention. ECGs were coded with respect to presence or absence of Q waves, signs of left ventricular hypertrophy or intraventricular conduction disturbances and ST segment elevation or depression ≥0.1 mV or T wave inversion, or both. *ECG changes* were defined as additional ST segment elevation or depression ≥0.1 mV or T wave deviation ≥0.1 mV versus that on the baseline ECG in the absence of pain.

Follow-up. Postdischarge data were obtained from municipal registries, clinical records, general practitioners and patients. Patients were followed up for a median of 94 months (range 85 to 100) for the occurrence of death, infarction, revascularization (coronary bypass or angioplasty) and hospital admission. Medication at 1, 3, 5 and 7 years was recorded.

Statistical analysis. Patient groups were compared with a Student *t* test for continuous variables and a chi-square test for categoric data. End points are presented in terms of "survival," "survival without myocardial infarction" and "infarction-free survival without revascularization." The probability of these end points is presented as Kaplan-Meier curves (8). Differences between curves were analyzed with log-rank tests (9). A stepwise Cox proportional hazards model was used to select predictors of (event-free) survival, specifically to relate the various Braunwald classes to prognosis. The following variables were considered: age; gender; history of myocardial infarction; hypertension; Braunwald classes I to III (severity), B and C (clinical circumstances); ECG changes; and intensity of medical treatment during the hospital period. All analyses were performed for the 282 patients with definite unstable angina.

Results

Patients. A total of 417 patients were enrolled in an observational study of suspected unstable angina, of whom 6 died in the hospital (6). The definite (final) diagnosis was unstable angina in 282 patients (68%) and acute myocardial infarction in 26; 109 patients (26%), the symptoms were attributed to other or nonspecific causes. The median age of patients with unstable angina was 63 years (range 31 to 89), 64% were men, 46% had a previous infarction, 23% had a history of unstable angina, and 27% had undergone previous revascularization (coronary artery bypass graft surgery [CABG] in 15%, percutaneous transluminal coronary angioplasty [PTCA] in 12%). Of the 282 patients with a final diagnosis of unstable angina, 20% were assigned to Braunwald class I, 35% to class II and 45% to class III. A total of 16% were classified as having postinfarction angina (class C), and 63% had ECG changes. Complete 7-year follow-up information could be obtained for 278 patients (99%) with unstable angina. The median follow-up period was 94 months (range 6 to 100).

Medical therapy. Antianginal treatment (beta-blockers, nitrates or calcium channel blockers, alone or in combination) was prescribed for 87% of patients at hospital discharge and 65% at the end of the first year and decreased to 51% at 7 years. Extensive treatment (more than one antianginal drug) decreased from 35% at the end of the first year to 26% at 7 years. Aspirin was routinely prescribed in two-third of patients and did not change during follow-up. Long-term oral anticoagulant treatment during follow-up was frequent (13% to 19%). The use of cholesterol-lowering therapy increased from 2% at discharge to 29% at 7 years. After 7 years, 46% of patients were in Canadian Cardiovascular Society angina class I, 23% were in class II, 20% were in class III, and 11% were in class IV.

Postdischarge course. The initial course of the 282 patients after hospital discharge was complicated (Fig. 1). Myocardial infarction in the first year was observed in 31 patients (11%); the subsequent yearly infarction rate was low, ~1.9%. Revascularization procedures were performed predominantly during the first year. PTCA or CABG or both, was performed in 141 patients (50%) at 7 years. Survival rates at 1, 3, 5 and 7 years were, respectively, 94%, 88%, 81% and 76%. The mortality between the first and seventh year averaged 3.4%/year, 1.2% higher than the standardized mortality rate for the general population of the same age. Survival without infarction and infarct-free survival without intervention are shown as Kaplan-Meier curves for the different subgroups (Fig. 2). Long-term and infarct-free survival were similar with respect to severity (Braunwald classes I to III). Early urgent intervention (<1 month), especially angioplasty, was particularly frequent in class III patients, whereas interventions for class I patients

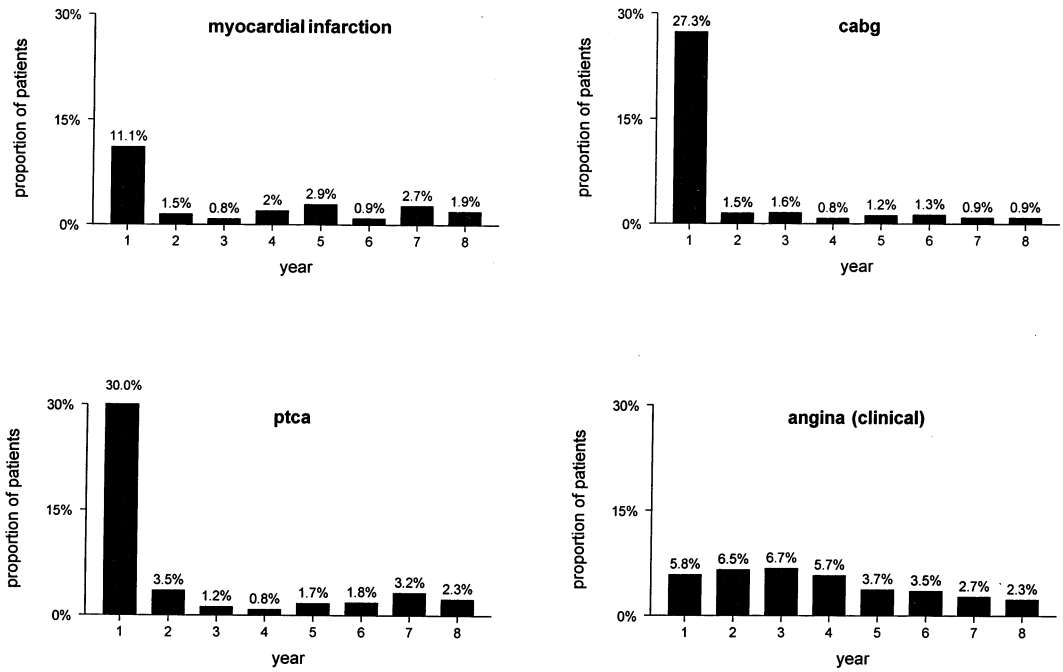

Figure 1. Proportion of events in 282 patients with unstable angina.

were spread throughout the first year. After 1-year follow-up, infarct-free survival without intervention was similar in classes I and III. Class II patients (no angina at rest within 48 h) had fewer interventions in the first year after hospital discharge. However, in contrast to classes I and III, interventions were performed with a constant rate during the total follow-up period. Thus, after 7 years, the rates were similar in all severity classes. Survival without infarction or CABG and without PTCA was significantly higher ($p < 0.05$) in patients with primary unstable angina (class B) than in postinfarction patients (Fig. 3). No significant differences were observed in event-free survival when the patient group was classified with respect to the presence or absence of ECG changes during the hospital period (Fig. 4).

Predictors of 7-year outcome. The only predictors of 7-year mortality by univariable analysis were age (≥70 years) and diabetes (Table 1). For all three outcomes (death; death or infarction; death or infarction or intervention), the adjusted risk ratios were estimated using the Cox proportional hazards model. Advanced age (≥70 years) and diabetes remained independent predictors of mortality (Table 1). Survival without infarction was related to age, diabetes and male gender. Angina at rest within 48 h (class III) and postinfarction angina (class C) were independent risk factors for the combined end point of survival, infarction or intervention, as were the use of two or more antianginal drugs during the hospital period and male gender.

Discussion

Long-term follow-up studies of patients with unstable angina are rare and date from more than two decades ago (1,10). Since then, the practice of cardiology and the definition of unstable angina have changed. We registered a well defined group of 282 consecutive patients with unstable angina from among 417 patients admitted to the hospital for chest pain. The selection of patients immediately after admission ensured that the whole spectrum of unstable angina was included in this registry. This inclusion is in contrast to most other studies of unstable angina that included only selected patients, restricted by age (11,12), absence of recent myocardial infarction or CABG, duration of pain episodes (13–15) or the presence of ischemic signs on the ECG (15–17). In most studies, patients were selected 24 to 48 h after admission, when myocardial infarction had been ruled out by serial enzyme analysis. In contrast, the only exclusion criteria in the present study were evidence of other disease assumed to be the cause of the chest pain and referral from other hospitals for further treatment of patients for whom a complete diagnosis already had been established.

Long-term outcome. To our knowledge the present data are the first to demonstrate that after a complicated first-year course, the long-term outcome of patients with unstable angina is good, with low subsequent rates of infarction and intervention. The mortality rate in the first year was 6% and 2% to 3% in the following years. Hospital admission because of chest pain at 1, 3, 5 and 7 years was, respectively, 5%, 4%, 3% and 2%. This good prognosis is comparable with that of other reports (2,12,15,18,19), although those studies were limited to 2 years of follow-up, and may be related to the high early

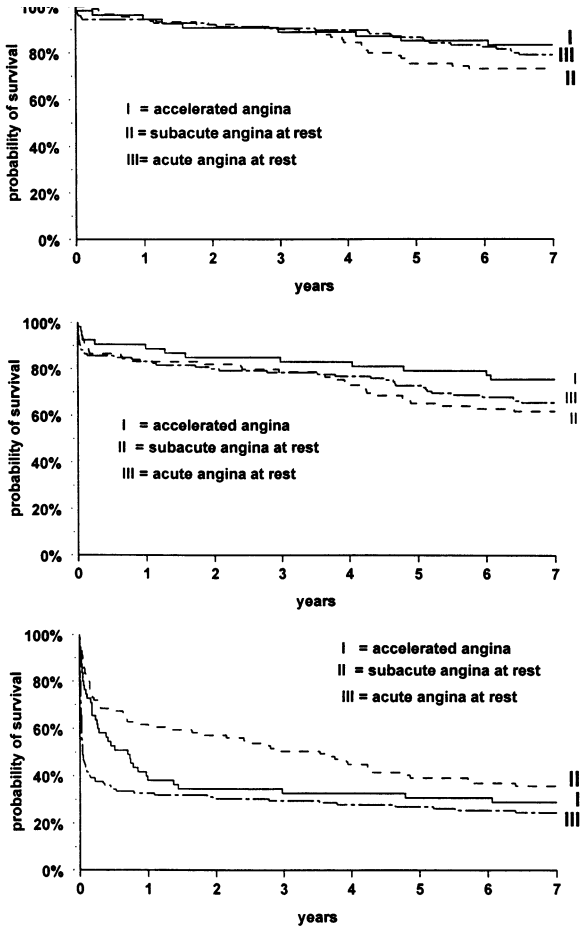

Figure 2. Rates of survival (**top**); survival without infarction (**middle**); and survival without infarction, CABG or PTCA (**bottom**) by class of severity in 282 patients with unstable angina.

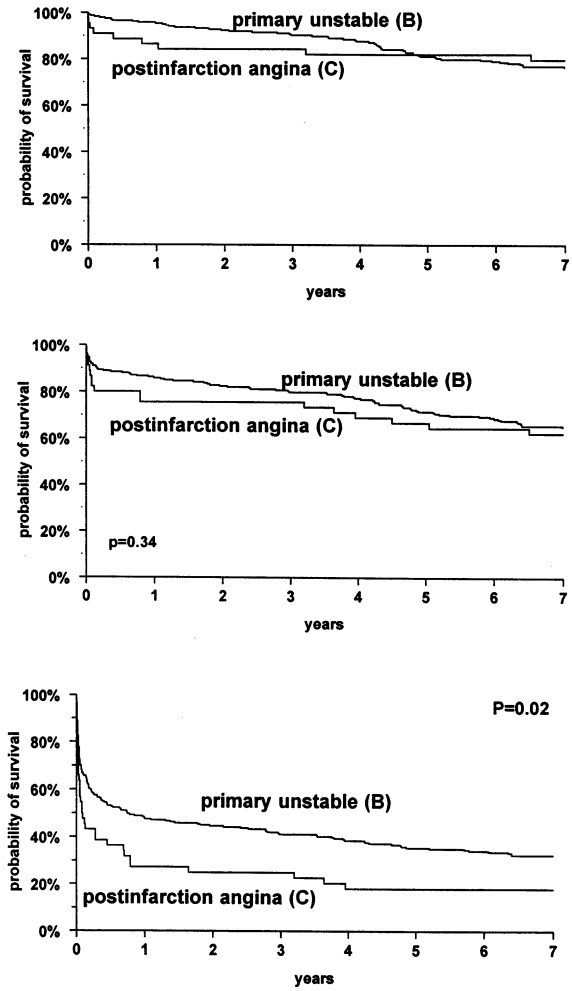

Figure 3. Rates of survival (**top**); survival without infarction (**middle**); and survival without infarction, CABG or PTCA (**bottom**) by clinical diagnosis in 282 patients with unstable angina.

intervention rate and improved medical therapy for this condition. Revascularization was particularly frequent during the hospital period and the subsequent first year, when 47% of patients underwent CABG or PTCA. The significant decrease in subsequent years is remarkable and reflects the "durability" of current revascularization techniques and effective antianginal therapy.

Medication and revascularization. Antianginal treatment remained frequent, with a constant group of 25% of patients taking two or more antianginal drugs (beta-blockers, calcium antagonists or nitrates). Most patients were taking aspirin (67%) or oral anticoagulant agents (17%). Most bypass procedures were performed in patients with accelerated angina without pain at rest (class I), whereas most coronary angioplasty procedures were performed in patients with angina at rest within 48 h (class III). Patients with angina at rest without pain within 48 h (class II) had a lower initial intervention rate than the other subgroups.

Braunwald classification. The Braunwald classification of unstable angina has been validated previously for short-term outcome (20–23) and appears to be appropriate for risk stratification in the first year when most events occur. However, at 7 years the event rates in all Braunwald classes were similar. In particular, the Braunwald classification had no long-term impact on mortality or infarction rates. However, patients with acute angina at rest (pain within 48 h [class III]) or postinfarction angina (class C) and patients with extensive antianginal treatment had high intervention rates, as might be expected. Quality of life might improve were revascularization performed earlier in patients with angina at rest without pain within 48 h (class II), although 30% of all patients survived for 7 years without intervention or infarction.

Conclusions. The Braunwald definitions appear to be appropriate for risk stratification, especially in the first year when most events occur. However, at 7 years the event rates were similar in all classes of unstable angina. The present study demonstrates that despite a complicated course during the first year, the long-term outcome is good in patients with unstable angina, with a high early intervention rate and low rates of infarction and intervention thereafter.

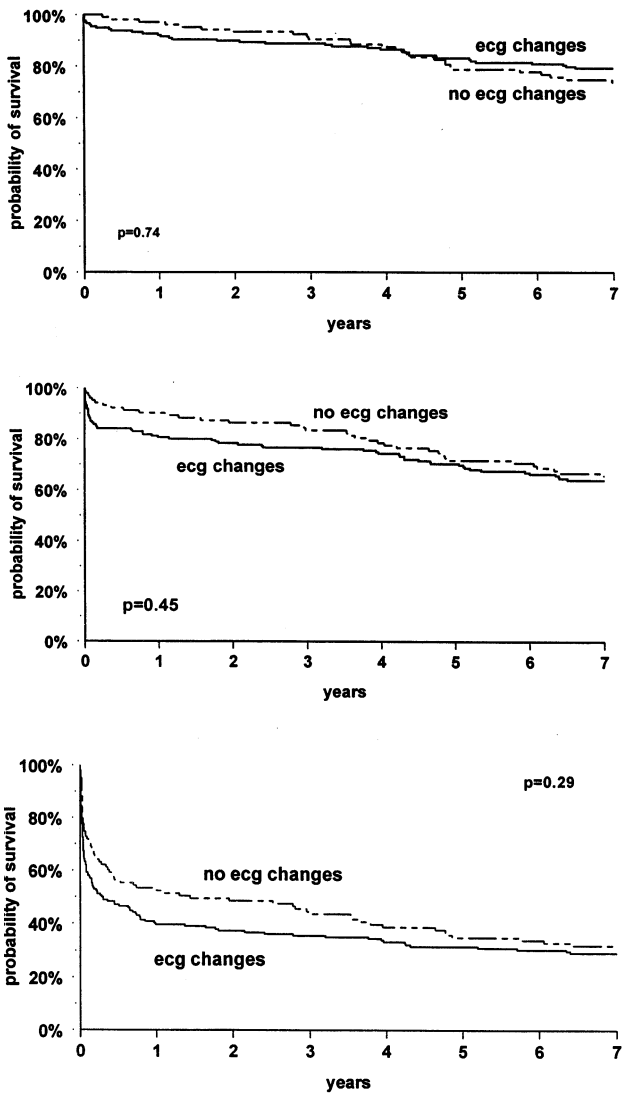

Figure 4. Rates of survival (**top**); survival without infarction (**middle**); and survival without infarction, CABG or PTCA (**bottom**) by ECG changes in 282 patients with unstable angina.

Table 1. Univariable and Multivariable Analysis: Predictors of Seven-Year Outcome in 282 Patients With Unstable Angina

	Univariable Analysis [RR (95% CI)]	Multivariable Analysis [RR (95% CI)]
Death		
Age ≥70 yr	2.83 (1.92–4.19)	4.22 (2.58–6.89)
Male gender	1.05 (0.69–1.60)	—
Diabetes	1.73 (1.10–2.72)	1.89 (1.07–3.36)
Braunwald classification		
Class II	1.85 (0.94–3.61)	—
Class III	1.68 (0.87–3.26)	—
Class C	0.77 (0.41–1.42)	—
ECG abnormalities	0.77 (0.51–1.13)	—
Extensive treatment*	1.40 (0.94–2.10)	—
Death or MI		
Age ≥70 yr	2.05 (1.39–3.01)	2.12 (1.42–3.17)
Male gender	1.19 (0.79–1.78)	1.46 (0.96–2.21)
Diabetes	2.30 (1.44–3.65)	2.09 (1.31–3.34)
Braunwald classification		
Class II	1.11 (0.74–1.66)	—
Class III	1.19 (0.81–1.74)	—
Class C	1.14 (0.69–1.89)	—
ECG abnormalities	0.95 (0.64–1.40)	—
Extensive treatment*	1.25 (0.84–1.85)	—
Death, MI or revasc		
Age ≥70 yr	0.83 (0.61–1.13)	—
Male gender	1.95 (1.44–2.66)	1.66 (1.25–2.78)
Diabetes	1.08 (0.73–1.59)	—
Braunwald classification		
Class II	0.60 (0.44–0.81)	—
Class III	1.70 (1.29–2.25)	1.66 (1.25–2.20)
Class C	1.62 (1.13–2.31)	1.62 (1.13–2.33)
ECG abnormalities	1.17 (0.87–1.55)	—
Extensive treatment*	1.46 (1.09–1.94)	1.35 (1.01–1.81)

*More than one antianginal drug (see Methods). CI = confidence interval; Class C = postinfarction angina; Class II = subacute angina at rest; Class III = acute angina at rest; ECG = electrocardiographic; RR = relative risk.

References

1. Gazes PC, Mobley EM Jr, Faris HM Jr, Duncan RC, Humphries GB. Preinfarction (unstable) angina—a prospective study—ten year follow-up. Prognostic significance of electrocardiographic changes. Circulation 1973;48: 331–7.
2. Mulcahy R, Al Awadhi AH, de Buitleor M, Tobin G, Johnson H, Contoy R. Natural history and prognosis of unstable angina. Am Heart J 1985;109:753–8.
3. Wilcox I, Freedman SB, Allman KC, et al. Prognostic significance of a predischarge exercise test in risk stratification after unstable angina pectoris. J Am Coll Cardiol 1991;18:677–83.
4. Sharma GV, Deupree RH, Luchi RJ, Scott SM. Identification of unstable angina patients who have favorable outcome with medical or surgical therapy (eight-year follow-up of the Veterans Administration Cooperative Study). Am J Cardiol 1994;74:454–8.
5. Braunwald E. Unstable angina: a classification. Circulation 1989;80:410–4.
6. van Miltenburg-van Zijl AJ, Simoons ML, Veerhoek RJ, Bossuyt PM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. J Am Coll Cardiol 1995;25:1286–92.
7. Gorlin R, Fuster V, Ambrose JA. Anatomic-physiologic links between acute coronary syndromes. Circulation 1986;74:6–9.
8. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
9. Peto R, Pike M. Conservation of the approximates (O-E)2/E in the log rank test for survival data or tumor incidence data. Biometrics 1973;29: 579–584.
10. Parisi AF, Khuri S, Deupree RH, Sharma GV, Scott SM, Luchi RJ. Medical compared with surgical management of unstable angina: 5-year mortality and morbidity in the Veterans Administration Study. Circulation 1989;80: 1176–89.
11. de Feyter P, Serruys W. Coronary angioplasty for patients with unstable angina pectoris. In: Topol E, editor. Acute Coronary Intervention. New York: Alan R. Liss, 1988:215–29.
12. Wilcox I, Freedman SB, McCredie RJ, Carter GS, Kelly DT, Harris PJ. Risk of adverse outcome in patients admitted to the coronary care unit with suspected unstable angina pectoris. Am J Cardiol 1989;64:845–8.
13. Olson HG, Lyons KP, Aronow WS, Stinson PJ, Kuperus J, Waters HJ. The high-risk angina patient: identification by clinical features, hospital course, electrocardiography and technetium-99m stannous pyrophosphate scintigraphy. Circulation 1981;64:674–84.
14. Heng MK, Norris RM, Singh BM, Partridge JB. Prognosis in unstable angina. Br Heart J 1976;38:921–5.
15. The Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research

Group. Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. Br Heart J 1986;56:400–13.

16. Ouyang P, Brinker JA, Mellits ED, Weisfeldt ML, Gerstenblith G. Variables predictive of successful medical therapy in patients with unstable angina: selection by multivariate analysis from clinical, electrocardiographic, and angiographic evaluations. Circulation 1984;70:367–76.
17. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396–403.
18. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105–11.
19. Balsano F, Rizzon P, Violi F, et al. Antiplatelet treatment with ticlopidine in unstable angina: A controlled multicenter clinical trial (the Studio della Ticlopidina nell'Angina Instabile Group). Circulation 1990;82:17–26.
20. Dini FL, Volterrani C, Giaconi A, Azzarelli A, Lunardi M, Benardi D. Prior myocardial infarction and prognostic outcome in patients with unstable angina in a post-discharge follow-up. Angiology 1996;47:321–7.
21. Calvin JE, Klein LW, VandenBerg BJ, et al. Risk stratification in unstable angina. Prospective validation of the Braunwald classification. JAMA 1995; 273:16–41.
22. Kleiman NS, Anderson HV, Rogers WJ, Theroux P, Thompson B, Stone PH. Comparison of outcome of patients with unstable angina and non-Q-wave acute myocardial infarction with and without prior coronary artery bypass grafting (Thrombolysis in Myocardial Infarction III registry). Am J Cardiol 1996;77:227–31.
23. Gandhi MM, Lampe FC, Wood DA. Incidence, clinical characteristics, and short-term prognosis of angina pectoris. Br Heart J 1995;73:193–8.